



PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

NICOLAU ET AL.

Serial No. 10/783,699

Filed: February 20, 2004

For: METHODS AND COMPOSITIONS COMPRISING
NON-PEPTIDE SMALL MOLECULES THAT
SOLUBILIZE THE ALZHEIMER'S A β PEPTIDE FIBER

**SUBMISSION OF FORMAL DRAWINGS AND
PETITION TO ACCEPT COLOR DRAWINGS**

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Responsive to the Notice to File Missing Parts of Nonprovisional Application mailed May 14, 2004 requiring the submission of new drawings in the patent application identified above, the applicant encloses herewith five (5) sheets of formal drawings.

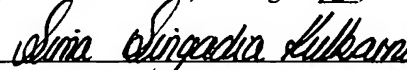
Applicants herewith petition for the acceptance of color drawings in the above-referenced patent application. Attached hereto are three (3) sets of color drawings for examination, copying and archival purposes. Figures 1, 3 and 4 are submitted in color since color drawings are the only practical medium by which to disclose the subject matter sought to be patented. A black and white copy of these color figures is also attached. Figures 2 and 5 are in black and white. Accordingly, we respectfully request that the petition submitted under 37 C.F.R. § 1.183 for waiver of the requirements of 37 C.F.R. § 1.84(a) be granted.

08/17/2004 FFANAI2 00000012 10783699

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mailstop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on August 13, 2004.


Sima Singadia Kulkarni - Reg. No. 43,732

The petition fee of \$130.00 required by 37 C.F.R. § 1.183 (§1.17(h)) to waive the requirements of Section 1.84 is attached hereto.

Please charge any additional fees, or credit any overpayment, to Deposit Account 11-0855. A duplicate copy of this sheet is attached.

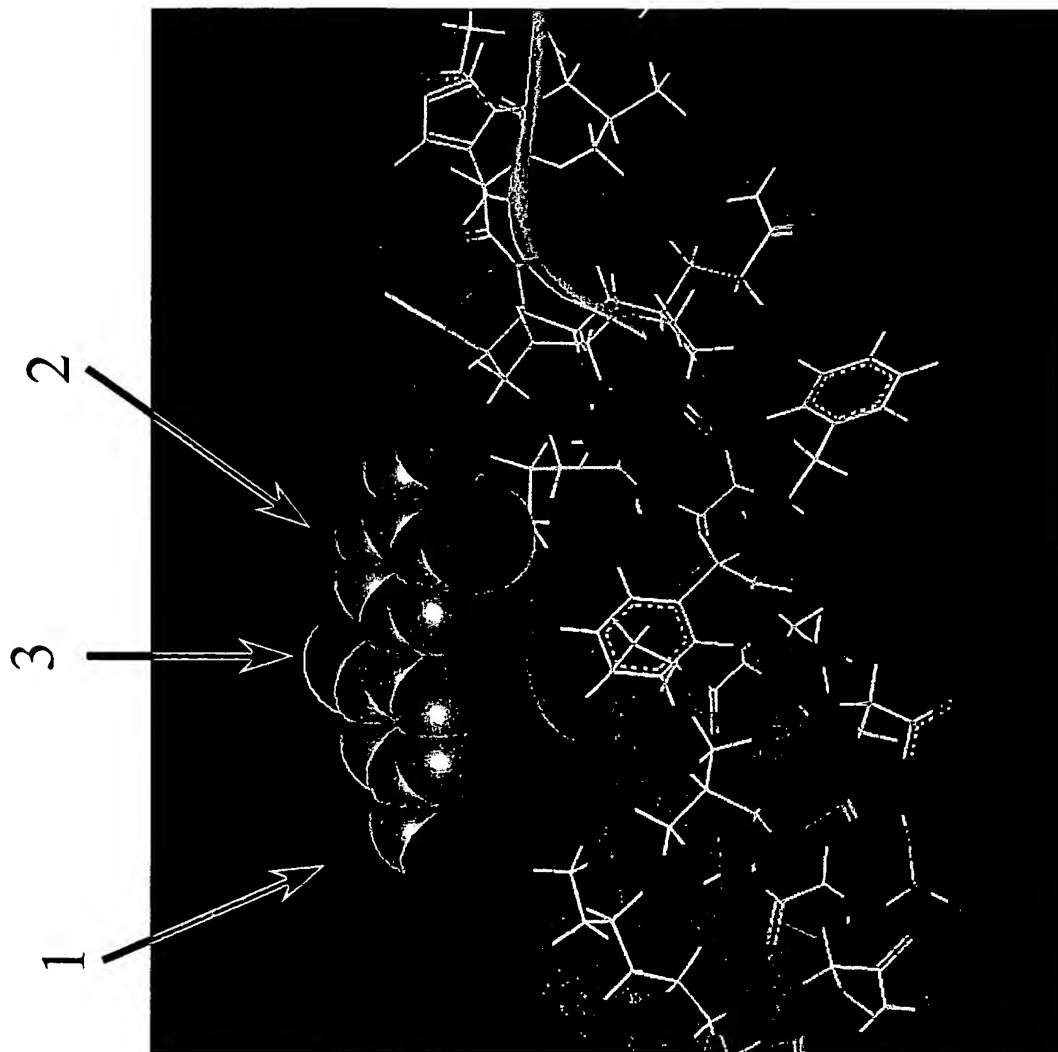
Respectfully submitted,

A handwritten signature in black ink, reading "Sima Singadia Kulkarni". The signature is written in a cursive, flowing style.

Sima Singadia Kulkarni
Reg. No. 43,732

KILPATRICK STOCKTON LLP
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Suite 2800
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Our Docket: 54341-0211 (297751)

Chemical Approach to Combinatorial Discovery Of β -sheet-Breaking Small Molecules



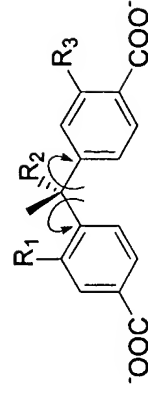
- 1 – Helix stabilization by selective electrostatic interactions
- 2 – Helix stabilization via interaction with the rigid hydrophobic scaffold
- 3 – Combinatorially varied substituents

Figure 1



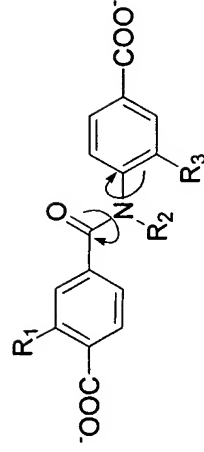
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“Morphomer” concept



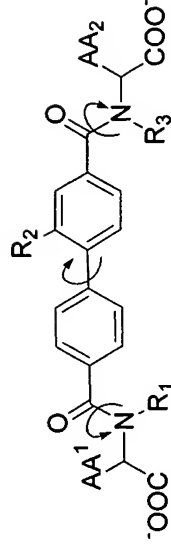
1

- Molecular scaffolds are designed complementary to A β helical (soluble) structure



2

- Conformational restrictions are introduced to partially lock each set of conformations (*morphology*) of library components



3

- Libraries formed on the basis of scaffolds explore both chemical (Rx) and conformational diversity space

Figure 2

Molecular Adaptation of Morphomers to the Target Leads to Formation of Stronger Complexes

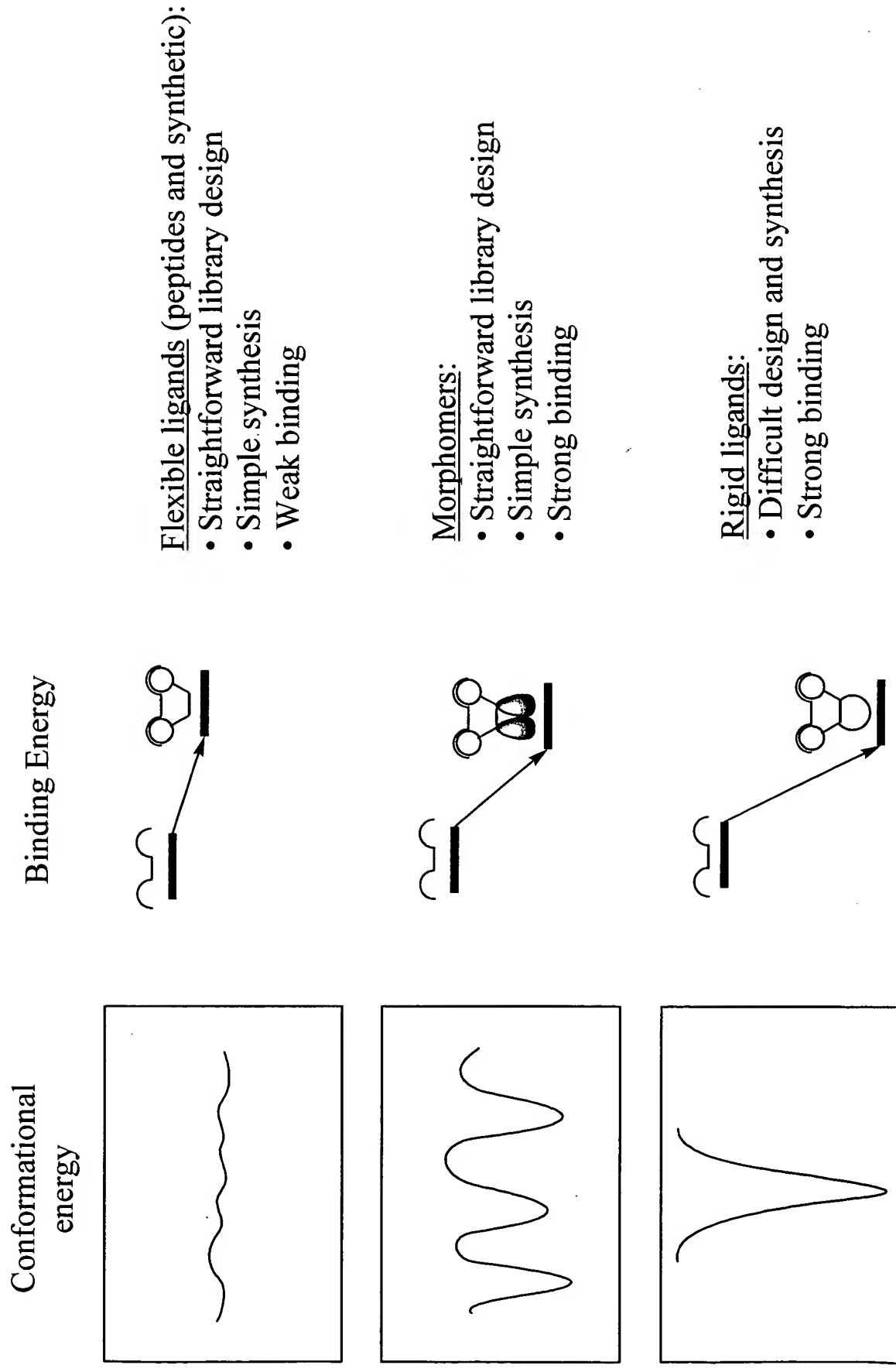


Figure 3

General Strategy of Small Molecules – β -Sheet breakers for Therapy of Alzheimer's Disease

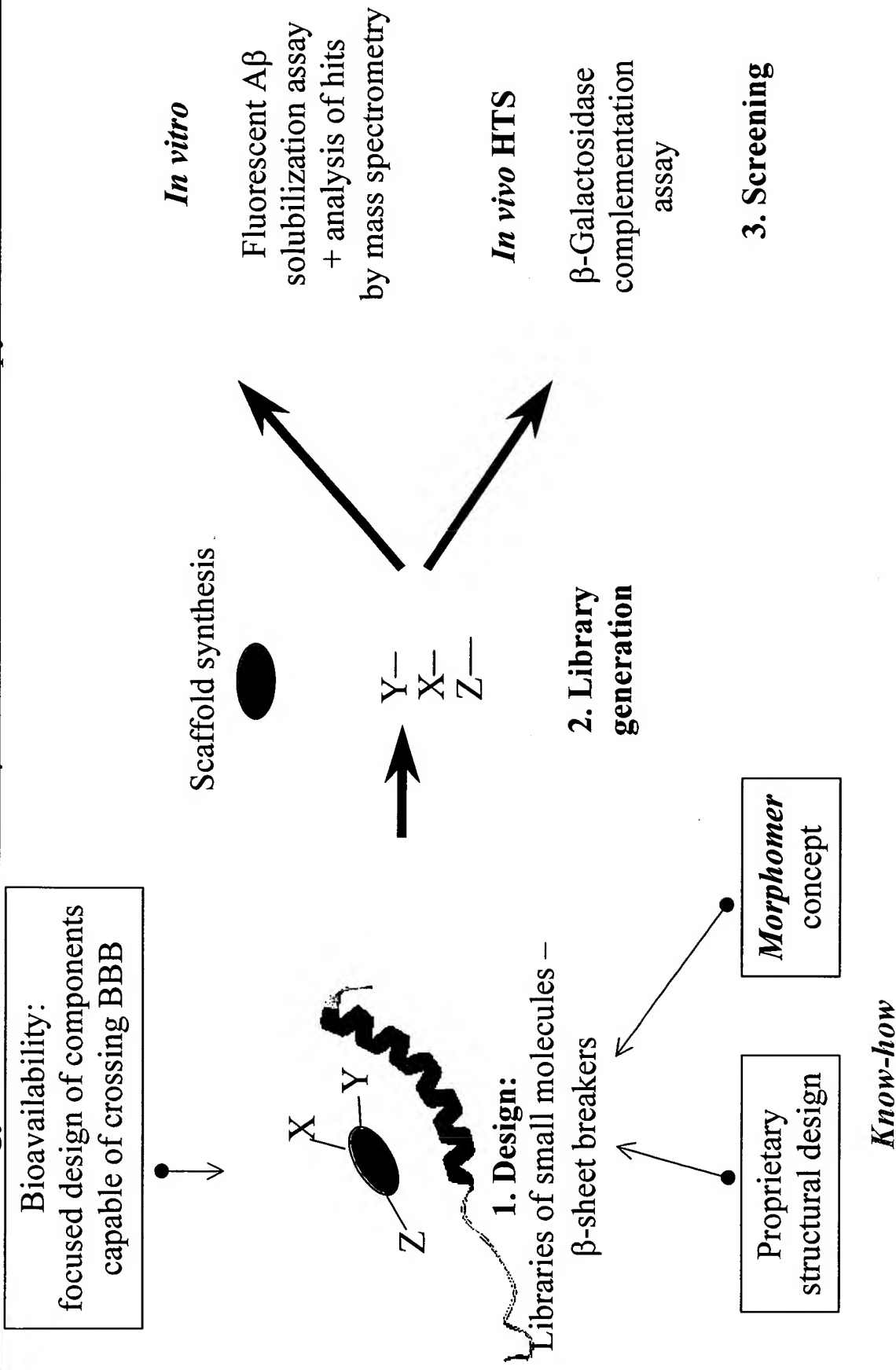


Figure 4

Screening of Small Molecules for A β Solubilization Activity

In vitro

- **Fluorescent Assay:**

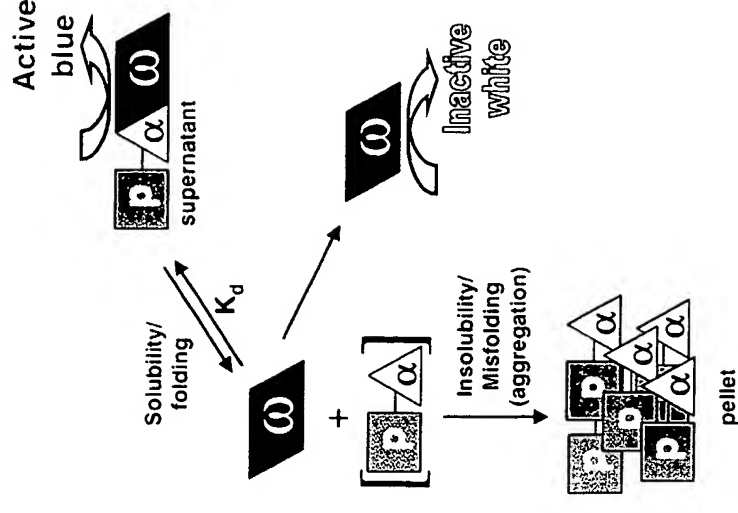
A β fiber stained with Thioflavin T solubilization/depolymerization is monitored by fluorescence decrease

- **Mass spectrometry assay:**

Complexes of amyloid with small molecules are detected and characterized by MS

Hits are fully structurally characterized using regiochemical tagging techniques (*provisional patent application filed*)

In vivo



in vivo solubilization assay for A β
(W.C. Wigley, et al.
Nature Biotechnol. 2001, 19, 131-136)

Figure 5